



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>A61K 31/40 // (A61K 31/40, 31:00, 38:00)</b>		<b>A1</b>	(11) International Publication Number: <b>WO 95/28926</b> (43) International Publication Date: 2 November 1995 (02.11.95)
(21) International Application Number: PCT/IB95/00332		(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
(22) International Filing Date: 21 April 1995 (21.04.95)			
(30) Priority Data: 08/231,969 21 April 1994 (21.04.94) US 08/253,938 2 June 1994 (02.06.94) US 08/327,478 21 October 1994 (21.10.94) US 08/340,416 15 November 1994 (15.11.94) US		Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(71) Applicant: SCHERING AKTIENGESELLSCHAFT [DE/DE]; Berlin-Wedding, Muellerstrasse 178, D-13342 Berlin (DE).			
(71)(72) Applicant and Inventor: PEREZ, H., Daniel [US/US]; 215 McAllister Avenue, Kentfield, CA 94904 (US).			
(72) Inventors: WACHTEL, Helmut; Suarezstrasse 22, D-14057 Berlin (DE). LÖSCHMANN, Peter-Andreas; Leon- Schmalzbach-Weg 7, D-7450 Hechingen (DE). GRAF, Hermann; Olwenstrasse 62, D-13465 Berlin (DE). HEDG- PETH, Joel; 33 Robinhood, San Francisco, CA 94127 (US).			
(74) Agent: HEANEY, Brion, P.; Millen, White, Zelano & Brani- gan, P.C., Arlington Courthouse Plaza 1, Suite 1400, 2200 Clarendon Boulevard, Arlington, VA 22201 (US).			
(54) Title: PDE IV INHIBITORS FOR TREATING MULTIPLE SCLEROSIS			
(57) Abstract			
<p>The present invention is a method of preventing or ameliorating the episodic recurrence of MS, comprising administering an effective amount of selective phosphodiesterase inhibitors of Type IV, e.g., Rolipram, e.g., wherein the severity of the episodic recurrences is ameliorated or the time period between episodes is lengthened. The present invention also relates to a pharmaceutical composition for treating MS comprising an effective amount of a combination of a PDE IV inhibitor and an anti-inflammatory or immunomodulatory drug in a pharmaceutically acceptable carrier.</p>			

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PDE IV inhibitors for treating multiple sclerosis

Background of the Invention

Demyelinating diseases are severe afflictions of the brain and spinal cord, involving the destruction of the myelin sheath which surrounds nerve fibers. As a result of demyelination, various neurological symptoms are manifested, including motor impairment, visual loss, and sensory changes. Multiple sclerosis (MS) is the most common of the demyelinating diseases. It is a disease characterized by episodes of focal disorder of the optic nerves, spinal cord, and brain. It is a severe chronic disabling disease with characteristic demyelination in the CNS triggered by probable autoimmune mechanisms in a genetically susceptible population. Typically, it produces recurring episodes of neurologic dysfunction, followed by remission (relapsing-remitting), but it may also be chronic. Although MS is a well-studied disease, its precise cause remains undetermined. One explanation is that an environmental factor which most often acts in childhood activates a specific population of T-cells (with the potential of attacking myelin-associated antigens such as MBP, MAP, MOP or others) which normally is controlled by suppressor-cells. In many MS cases, non-specific stress results in disease exacerbations with opening of the BBB, edema, immigration and activation of T-cells and macrophages and subsequent destruction of oligodendroglia- associated myelin followed by failing attempts at remyelination and finally a glia scar (relapsing - remitting form of MS). These exacerbations which can be visualized by MRI are associated, depending on location, with severe functional disabilities;

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furthermore, with an increasing number of relapses, the disease (and the antigen being attacked) becomes more generalized and progresses with less clearcut intervals (progressive form of MS, secondary or primary) and increasing 5 and persisting disability which causes (in this mostly young population) impairment of life qualify with loss of employment and independent life (with hospitalization and eventually death).

Until recently, treatments have been empirical and not 10 entirely successful. See Cecil's Textbook of Medicine (Wyngaarden, 1993). Classic non-specific immunosuppressive therapies (including corticosteroids) and cytostatic drugs as a rule have failed to alter this sequence of events and 15 disease progression - possibly because they are poorly tolerated in these patients and also because they inhibit endogenous immunosuppressive mechanisms as well. For a review of treatments, e.g., see *Principles of Neurology*, Fifth Edition, (Adams et al., 1993). Recently non-specific 20 immunomodulatory therapy with interferon- $\beta$ -1b has been shown to prolong disease-free intervals in patients with beginning relapsing/remitting MS; however, in the great majority of 25 these patients, exacerbations cannot be prevented completely, and also the effect on disability during the first three years of therapy is still small. Corticosteroid therapy relieves some acute symptoms of these exacerbations (probably by reducing edema) but does not affect long term prognosis. However, it appears of utmost importance to suppress all 30 exacerbations with their activation, extension and amplification of autoimmune mechanisms which make the disease uncontrollable and disabling. There remains a need for additional drugs which have an effect on the disease's severity and progression.

#### Summary of the Invention

Recent advance in the clinical, biochemical and imaging 35 technologies enable clinicians to predict and diagnose such exacerbations in a very early stage, and thus, it now becomes

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possible to combine different therapeutic strategies to achieve a maximal therapeutic effect. Immunomodulatory therapies with non-specific mechanisms, e.g., with interferon- $\beta$ -1b (or specific immunomodulatory drugs such as copolymer I, as well as inducing tolerance to MS antigens) which will never work to 100% as they need to be given before the onset of the disease, but they can reduce to a clear and significant degree the number of clinical exacerbations and, even more, of lesions in the brain. Fortunately, for the target of bringing disease activity to a complete hold, the new diagnostic techniques being developed have the potential to detect the very early beginning of an exacerbation (e.g., increases in  $\gamma$ -interferons, TNF- $\alpha$ , increased number of activated specific T-cells in the blood, new specific MRI and other imaging techniques, and clinical observation). Therefore, strong and efficient drugs are necessary which act not just on some symptoms of the exacerbation but are able to prevent them completely and thus, inhibit disease progression. However, also new therapeutic strategies which aim, e.g., at peripheral T-cell activation, endothelial adhesion, opening of blood-brain barrier and activation of the T-cell-macrophage/-microglia interaction with subsequent oligodendrocyte damage and demyelination do affect defense mechanisms not just in the autoimmune condition but, on chronic use, are also damaging vital defense mechanism against exogenous (e.g., bacterial, parasitic or viral infections) as well as against endogenous harmful agents and effects (e.g., tumorigenesis).

An aspect of the present invention is to combine well tolerated chronic maintenance therapy with the use of new diagnostic techniques to predict or detect early exacerbations which can then, but only then, be treated aggressively by a number of drugs, or their combinations, to ensure that no persistent CNS lesions can be produced with their fatal influence on disease exacerbation, extension and progression. Furthermore, combination of therapies with different mechanisms to achieve maximum efficacy will improve tolerability of therapy (as the effects of interferon- $\beta$ -1b in

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MS have been shown to be dose-dependent, higher dosages could be expected to achieve higher and even 100% efficacy, but increasingly severe side effects prevent this type of treatment), and finally, these new combinations of maintenance 5 and anti-exacerbation therapies result in a clearly reduced risk of side effects which can be caused by high-dose and long-term use of these drugs in monotherapy. Indeed when basic maintenance therapy is being combined with the use of these new strategies only when needed (e.g., during or just 10 before an exacerbation) less side effects of both complementary and synergistic therapeutic lines do occur and these forms of therapy can be combined to achieve an optimal clinical result. Also, in this new concept of short-term 15 therapy of exacerbations, different drugs can be combined to prevent further damage and disease progression. Thus, inhibition of synthesis of cytotoxic cyto- and chemokines can be combined with drugs which inhibit their release, and both may be enhanced in efficacy by, e.g., simultaneous inhibition 20 of traffic across the blood-brain barrier, or with other drugs which inhibit - or even reverse - the ultimate tissue damage (e.g., nerve growth factors, calcipotriols, calpain inhibitors, etc.).

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		pathogenic cascade	possible therapeutic intervention
1.-		activation of peripheral specific T-cells which are potentially autoreactive to myelin	destroy these T-cells reactivate tolerance by oral antigens, immune globulins? enhance suppressor mechanisms, e.g., interferon- $\beta$ -1b
2.-		enhanced blood-brain barrier permeability to these T-cells	close blood-brain barrier, e.g., by anti-adhesion molecules such as anti-integrin monoclonal antibodies
3.-		immigration of macrophages, and macrophage-T-cell-interaction and activation	interfere with T-cell receptors, enhance suppressor mechanisms, e.g., by interferon $\beta$ -1b
4.-		local inflammation and edema	non-specific anti-inflammatory and anti-edema strategies, e.g., corticosteroids
5	5.-	enhance release of $\gamma$ -interferons, TNF $\alpha$ and other cytotoxic cytokines	antagonize $\gamma$ -interferon, TNF $\alpha$ and other cytotoxic cytokines by acting on synthesis, release or other targets (e.g., receptors), e.g., be interferon $\beta$ -1b
	6.-	oligodendrocyte injury with acute myelin breakdown and degradation of axonal lamellae by microglia/macrophages	prevent myelin injury, e.g., with external competing antigens, such as CoP I
	7.-	acute conduction block, with functional impairment	act on ion channels, e.g., potassium channel blockers
	8.-	chronic de- and re-myelination process, functional adaptation and reorganization within the brain	enhance oligodendrocyte remyelination mechanisms, e.g., by glial growth factors, or Schwann cell implantation
10	9.-	persisting lesion without or with astrocyte scar and functional impairment, depending on size and location	symptomatic therapies against spasticity, fatigue, urinary problems, etc., therapeutic aids and training of remaining skills

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While many compounds can attack or another of these MS mechanisms and have, as a rule, typical risks and side effects associated with any specific mechanism, our experimental studies have, surprisingly, demonstrated that inhibitors of phosphodiesterase IV, such a rolipram, are very highly effective on human MS cells, as well as, in different animal models of the disease (e.g., EAE, EAN in different species); furthermore, in different human conditions, their safety and efficacy on different biological parameters has already been observed. With these combined mechanisms it is obvious that low dosages can be used which in monotherapy, or even more so in combination with other maintenance therapies, can be used to prevent relapses or reduce or treat exacerbations of MS with very minor side effects (in contrast to other therapies).

Furthermore, at the same or lower (exceptionally also higher) dosages these drugs can be combined with other compounds as described from 1-9 to achieve additive and synergistic therapeutic effects in order to achieve maximum efficacy (and thus inhibition of progression as described previously) with a minimum of side effects.

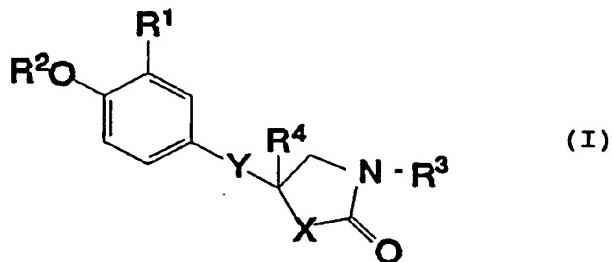
An aspect of the present invention thus relates to a method of treating or preventing MS comprising administering an effective amount of a combination of a Type IV phosphodiesterase inhibitor (PDE IV inhibitor) and antiinflammatory or immunomodulatory drugs.

The phosphodiesterase PDE inhibitors suitable for use in this invention are preferably cycloadenosine-3',5'-monophosphate (cAMP) PDE type IV (PDE IV) inhibitors according to the modern classification (J.A. Beavo and D.A. Reifsnyder, Trends Pharmacol. Sci. 11; 150-155, 1990) and include, but are not limited to compounds disclosed in U.S. 4,193,629, WO 92/02220; U.S. 4,186,129; EP 247 725; U.S. 5,064,854; N.A. Saccamono et al., J. Med. Chem. 34, 291-298, 1991; F.J. Vinick et al., J. Med. Chem. 34, 86-89, 1991; J. A. Lowe et al., J. Med. Chem. 34, 624-628, 1991; 1,3-dibutyl-3,7-dihydro-7-(2-oxopropyl)-1H-purin-2,6-dione(denbufylline, BRL 30892);

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- 4-[ (3-butoxy-4-methoxyphenyl)methyl]-2-imidazolidinone (RO20-1724);  
 5,6-diethoxybenzo[b]thiophen-2-carboxylic acid (tibenelast, LY 186655);  
 5 3-ethyl-1-(3-nitrophenyl)-2,4(1H,3H)-chinazolinedione  
 (nitraquazone, TVX 2706);  
 6-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazine-5-yl)-1-(3,4-dimethoxybenzoyl)-1,2,3,4-tetrahydro-4,4-dimethylchinoline (EMD 54622);  
 10 1-ethyl-4-[(1-methylethyliden)hydrazino]-1H-pyrazolo[3,4-b]pyridin-5-carboxylic acid ethylester (etazolate);  
 N-hydroxy-5,6-dimethoxy-benzo[b]thiophene-2-carboximidamide (Org 30029);  
 15 2-amino-6-methyl-4-propyl-(1,2,4)triazolo[1,5-a]pyrimidine-5(4H)-one (ICI 63197);  
 6-[4-(difluoromethoxy)-3-methoxyphenyl]-3(2H)-pyridazinone (zardaverine) pentoxifilline; propentofilline; vincocetine;  
 and the pharmaceutically acceptable salts thereof.

Preferred PDE IV inhibitors are racemic and optically active compounds of formula I



wherein

$R^1$  is  $C_{1-6}$ -alkyl, a heterocyclic ring, or  $OR^5$ ; and  
 $R^5$  is  $C_{1-6}$ -alkyl,  $C_{3-7}$ -cycloalkyl,  $C_{2-6}$ -alkenyl,

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C<sub>3-7</sub>-alkinyl, C<sub>3-7</sub>-cycloalkyl-C<sub>1-4</sub>-alkyl, aryl, aralkyl, a heterocyclic ring or C<sub>1-6</sub>-alkyl substituted by one or more halogen atoms, hydroxy, carboxy, C<sub>1-4</sub>-alkoxy, C<sub>1-4</sub>-alkoxycarbonyl, or an optionally alkyl substituted amino group;

5 R<sup>2</sup> is C<sub>1-4</sub>-alkyl, C<sub>2-4</sub>-alkenyl, or C<sub>2-4</sub>-alkinyl;

R<sup>3</sup> is a hydrogen atom, C<sub>1-6</sub>-alkyl, aryl, aralkyl, or aryl optionally substituted by one or two methyl groups or C<sub>1-6</sub>-alkanoyl;

10 R<sup>4</sup> is a hydrogen atom or C<sub>1-6</sub>-alkyl;

Y is a direct bond or a CH<sub>2</sub> group;

X is CH<sub>2</sub>, CH<sub>2</sub>-CH<sub>2</sub>, NH, or an oxygen atom; and the pharmaceutically acceptable salts thereof.

Preferred compounds of formula I are those wherein,

15 R<sup>2</sup> is methyl;

R<sup>3</sup> is a hydrogen atom or C<sub>1-6</sub>-alkanoyl;

R<sup>1</sup> is OR<sub>5</sub>; R<sub>5</sub> is C<sub>1-6</sub>-alkyl, C<sub>3-7</sub>-cycloalkyl, or 3-tetrahydrofuryl;

R<sup>4</sup> is hydrogen or C<sub>1-4</sub>-alkyl; and

20 X is a CH<sub>2</sub> group or oxygen.

Especially preferred compounds of formula I are those wherein R<sup>3</sup> is hydrogen.

Specifically exemplified is 4-(3-(cyclopentyloxy)-4-methoxyphenyl)-2-pyrrolidinone (rolipram).

25 The term "alkyl" as used herein include straight or branched alkyl radicals, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, pentyl, 2-methyl-butyl, 2,2-dimethylpropyl and hexyl.

30 By the term "alkenyl" as used herein is meant to include, but not limited to vinyl, 1-propenyl, 2-propenyl, 2-propinyl or 3-methyl-2-propenyl.

By the term "cycloalkyl" or "cycloalkyl alkyl" as used herein is meant to include groups of 3-7 carbon atoms, such as cyclopropyl, cyclopropylmethyl, cyclopentyl or cyclohexyl.

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By the term "aryl" or "aralkyl" as used herein is meant an aromatic ring or ring system of 6-10 carbon atoms, preferably monocycle, such as phenyl, benzyl, phenethyl or naphthyl.

5 By the term "heterocyclic ring" as used herein is meant a saturated ring of 5 to 6 members having a single oxygen, sulfur or nitrogen atom, such as, but not limited to 2- and 3-tetrahydropyran, 2- and 3-tetrahydrofuran, pyrrolidino, 2- and 3-pyrrolidyl, piperidinino, 2-, 3- and 4-piperidyl and  
10 the corresponding N-alkyl pyrrolidyl and piperidyl rings, wherein the alkyl is of 1-4 carbon atoms. Also encompassed within the scope of this invention are heterocyclic rings having more than one hetero atom such as morpholino, piperazino or N-alkyl piperazino.

15 By the term "halo" as used herein is meant all halogens, i.e., chloro, fluoro, bromo and iodo.

The preparation of the compounds of Formula I can be carried out by the procedure outlined in the above-mentioned  
20 patents or by U.S. Patent Nos. 4,153,713; 4,186,129; and 5,298,628; WO 86/02268; or EP 0 247 725. Rolipram is 4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidinone. See, e.g., Merck Index, 11th edition, pp. 1312-1313. Rolipram and related compounds can be prepared, e.g., according to U.S. Patent No. 4,193,926.

25 The anti-inflammatory and immunomodulatory drugs suitable for use in this invention include but are not limited to:

1. interferon derivatives, e.g., betaserone,  $\beta$ -interferon,  $\beta$ -interferon muteins;
2. prostane derivatives, e.g., compounds disclosed in  
30 PCT/DE93/0013, e.g., iloprost, cicaprost;
3. glucocorticoids, e.g., cortisol, prednisolone, methylprednisolone, dexamethasone;
4. immunsuppressives, e.g., cyclosporine A, FK-506, methoxsalene, thalidomide, sulfasalazine, azathioprine, methotrexate;
- 35 5. lipoxygenase inhibitors, e.g., zileutone, MK-886, WY-50295, SC-45662, SC-41661A, BI-L-357;

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6. leukotriene antagonists, e.g., compounds disclosed in DE 4009117; German patent application P 42 42 390.2; WO 9201675; SC-41930; SC-50605; SC-51146; LY 255283 (D.K. Herron et al., FASEB J; 2: Abstr. 4729, 1988); LY 223982 (D.M. Gapinski et al., J. Med. Chem. 33: 2798-2813, 1990); U-75302 and analogs, e.g., described by J. Morris et al., Tetrahedron Lett. 29: 143-146, 1988, C.E. Burgos et al., Tetrahedron Lett. 30: 5081-5084, 1989; B.M. Taylor et al., Prostaglandins 42: 211-224, 1991; compounds disclosed in U.S. 5,019,573; ONO-LB-457 and analogs, e.g., described by K. Kishikawa et al., Adv. Prostagl. Thrombox. Leukotriene Res. 21: 407-410, 1990; M. Konno et al., Adv. Prostagl. Thrombox. Leukotriene Res. 21: 411-414, 1990; WF-11605 and analogs, e.g., disclosed in U.S. 4,963,583; compounds disclosed in WO 9118601, WO 9118879; WO 9118880, and WO 9118883;
- 10 7. antiinflammatory substances, e.g., NPC 16570, NPC 17923 described by L. Noronha-Blab. et al., Gastroenterology 102 (Suppl.): A 672, 1992; NPC 15669 and analogs described by R.N. Burch et al., Proc. Nat. Acad. Sci. USA 88: 355-359, 1991; S. Pou et al., Biochem. Pharmacol. 45: 2123-2127, 1993;
- 15 8. peptide derivatives, e.g., ACTH and analogs; soluble TNF-receptors; TNF-antibodies; soluble receptors of interleukines, other cytokines, T-cell-proteins; antibodies against receptors of interleukines, other cytokines, T-cell proteins;
- 20 9. calcipotriols and their analogues as activators of syntheses of different nerve growth factors, or these growth factors themselves or small peptides thereof which stimulate oligodendrocyte growth (or prevent their apoptosis or destruction) and enhance remyelination.
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Our data show that in their effects on human MS cells as well as in different animal models of demyelinating disease (e.g., different EAE models) various of these new drugs can be combined successfully to achieve better protection with less side effects.

By "immunodulatory drugs", it is meant, e.g., agents which act on the immune system, directly or indirectly, e.g., by stimulating or suppressing a cellular activity of a cell in the immune system, e.g., T-cells, B-cells, macrophages, or other APC cells, or by acting upon components outside the immune system which, in turn, stimulate, suppress, or modulate the immune system, e.g., hormones, receptor agonists or antagonists, and neurotransmitters; immunomodulators can be, e.g., immunosuppressants or immunostimulants.

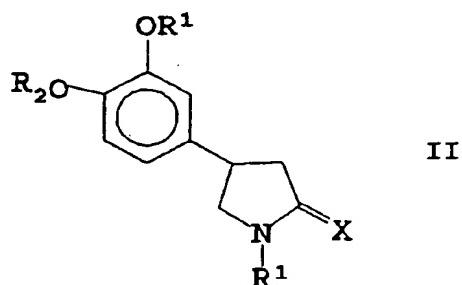
By "anti-inflammatory drugs", it is meant, e.g., agents which treat inflammatory responses, i.e., a tissue reaction to injury, e.g., agents which treat the immune, vascular or lymphatic systems.

Again, in this new combined therapeutic strategy, there are also many steps where the presumed cascade of MS can be attacked by existing or future drugs (see simplified schedule) after the initial specific or non-specific causes, which include impairment of suppressor T-cell effects on myelin-specific autoimmune T-cells:

The present invention also relates to a method of treating or preventing MS, comprising administering an effective amount of compound of formula I or II alone, preferably Rolipram, a Type IV phosphodiesterase.

The invention, in one aspect, relates to racemates and optically active 4-(polyalkoxyphenyl)-2-pyrrolidones of formula II which are useful in preventing or treating multiple sclerosis:

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wherein R<sub>1</sub> and R<sub>2</sub> each are alike or different and are hydrocarbon of up to 18 carbon atoms with at least one being other than methyl, a heterocyclic ring, or alkyl of 1-5 carbon atoms which is substituted by one or more of halogen atoms, hydroxy, carboxy, alkoxy, alkoxy carbonyl or an amino group; R' is a hydrogen atom, alkyl, aryl or acyl; and X is an oxygen atom or a sulfur atom.

These compounds and the methods of making them are described, e.g., in U.S. Patent No. 4,193,926 and WO 92/02220.

A preferred compound according to the present invention is Rolipram. Rolipram is 4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidinone. See, e.g., *Merck Index*, 11th edition, pages 1312-1313. It is commercially available from Schering AG, Berlin, Germany, or may be prepared, e.g., according to Belgian Patent No. 826,923 or U.S. Patent No. 4,193,926. It is useful conventionally as an antidepressant, e.g., U. Schwabe et al., *Mol. Pharmacol.* 12, 900 (1976); H. Wachtel, *Neuropharmacol.* 22, 267 (1983); H. Wachtel and H. Schneider, *Neuropharmacol.* 25, 1119 (1986); W. Krause and G. Kühne, *Xenobiotica* 18, 561 (1988). Clinical evaluation of Rolipram for depression is reported in E. Zeller et al., *Pharmacopsychiatry* 17, 188 (1984). A comparative clinical trial with amitriptyline, q.v. in severe depressions is reported in F. Eckmann et al., *Curr. Ther. Res.* 43, 291 (1988). Derivatives of Rolipram can also be used according to the invention, i.e., compounds which are structurally related to Rolipram, and are effective in preventing and/or treating MS, e.g., those of formula I.

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The present invention also generally relates to the use of a Type IV phosphodiesterase inhibitor, preferably a compound of formula I, especially Rolipram, in multiple sclerosis (MS), for preventing, and/or ameliorating the severity, symptoms, and/or periodicity of recurrence of the disease, e.g., lengthening the time period between episodes in which symptoms flare, and/or suppressing the ongoing immune or autoimmune response associated with the disease.

The invention thus relates to the administration of an effective amount of such a compound, e.g., one according to formula I or II, preferably Rolipram, to a patient to prevent or treat MS. The amount of said compound, e.g., Rolipram, administered is an amount which is effective, for example, in preventing or ameliorating the symptoms of the disease or the disease's recurrence, or affecting the ultimate course of the disease, e.g., blocking the inflammatory response in the brain, the appearance of inflammatory lesions, neuronal or neuroglia cell death, and/ or demyelination and the symptoms typically associated with pathogenesis of the disease.

The present invention also provides pharmaceutical compositions comprising a compound according to formula I or II, preferably a Type IV phosphodiesterase inhibitor, preferably Rolipram, or combinations of drugs as described above, which are useful in preventing or treating multiple sclerosis. According to the method, a compound of formula I or II, or drug combinations, can be administered, e.g., in a single dose, in multiple doses, e.g., through-the-skin injection or by sustained release means such as an implanted osmotic pump.

According to the present invention, a pharmaceutical composition of Formulae I and II, or combinations as described above, comprising an effective amount of each compound described can be administered to patients having multiple sclerosis, e.g., multiple sclerosis variants such as Neuromyelitis Optica (Devic's Disease), Diffuse Sclerosis, Transitional Sclerosis, Acute Disseminated Encephalomyelitis, and Optic Neuritis.

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Symptoms of MS which are prevented or ameliorated or treated include: weakness and/or numbness in one or more limbs; tingling of the extremities and tight band-like sensations around the trunk or limbs; dragging or poor control of one or both legs to spastic or ataxic parepesis; hyperactive tendon reflexes; disappearance of abdominal reflexes; Lhermitte's sign; retrobulbar or optic neuritis; unsteadiness in walking; brain stem symptoms (diplopia, vertigo, vomiting); disorders of micturition; hemiplegia; trigeminal neuralgia; other pain syndromes; nystagmus and ataxia; cerebellar-type ataxia; Charcot's triad; diplopia; bilateral internuclear ophthalmoplegia; myokymia or paralysis of facial muscles; deafness; tinnitus; unformed auditory hallucinations (because of involvement cochlear connections); vertigo and vomiting (vestibular connections); transient facial anesthesia or of trigeminal neuralgia; bladder dysfunction; euphoria; depression; dementia, dull, aching pain in the low back; sharp, burning, poorly localized pains in a limb or both legs and girdle pains; abrupt attacks of neurologic deficit; dysarthria and ataxia; paroxysmal pain and dysesthesia in a limb; flashing lights; paroxysmal itching; and/or tonic seizures, taking the form of flexion (dystonic) spasm of the hand, wrist, and elbow with extension of the lower limb. A patient having MS may have one or more of these symptoms or other clinical manifestations typically associated with MS and one or more can be ameliorated by administrating of compounds according to the present invention.

The administration of Type IV phosphodiesterase inhibitors such as Rolipram, or combinations of the latter other drugs, can also block or reduce the physiological and pathogenic deterioration associated with MS, e.g., inflammatory response in the brain and other regions of the nervous system, breakdown or disruption of the blood-brain barrier, appearance of lesions in the brain, tissue destruction, demyelination, autoimmune inflammatory response, acute or chronic inflammatory response, neuronal death, and/or neuroglia death.

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The active agents of this invention are useful to treat the different types of MS, including the multifocal, CNS, relapsing and remitting course; the multifocal, CNS, progressive course; the single-site, relapsing and remitting course; and other variants of multiple sclerosis. See, e.g., Cecil's Textbook of Medicine, edited by James B. Wyngaarden, 1988.

Effects of the administration of Rolipram and other Type IV phosphodiesterase inhibitors, and combinations of it with other drugs include, e.g., preventing the disease, ameliorating symptoms of the disease, reducing the annual exacerbation rate (i.e., reducing the number of episodes per year), slowing the progression of the disease, or reducing the appearance of brain lesions (e.g., as identified by MRI scan). The episodic recurrence of the mentioned diseases such as MS can be ameliorated, e.g., by decreasing the severity of the symptoms (such as the symptoms described above) associated with the, e.g., MS episode, or by lengthening the time period between the occurrence of episodes, e.g., by days, weeks, months, or years, where the episodes can be characterized by the flare-up and exacerbation of disease symptoms, or preventing or slowing the appearance of brain inflammatory lesions. See, e.g., Adams, R.D., Principles of Neurology, 1993, page 777, for a description of a neurological inflammatory lesion.

Other specific, suitable, non-limiting examples of Type IV phosphodiesterase inhibitors which can be employed in this invention include compounds described in WO93/19068, compounds RO 20-1724 (4-[(3-butoxy-4-methoxyphenyl)methyl]-2-imidazolidinone), ICI 63197 (2-amino-6-methyl-4-propyl[1,2,4]triazolo[1,5-a]pyrimindin-5(4H)-one), denbufylline and etazolate.

By "Type IV phosphodiesterase inhibitor", "specific Type IV phosphodiesterase inhibitor", and similar expressions are meant a selective, i.e., specific, such inhibitor, where the compound binds to or inhibits preferentially the Type IV phosphodiesterase when compared to known types of

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phosphodiesterase types, e.g., I, II, or III, e.g., whereby the compound has a lower IC<sub>50</sub> (more potent) for the Type IV phosphodiesterase, such as where the IC<sub>50</sub> is, e.g., 2-fold, 5-fold, 10-fold, 50-fold, or more potent, for the Type IV phosphodiesterase compared to another known type of phosphodiesterase, e.g., I, II, or III. Such selectivity of a compound according to the present invention for a Type IV phosphodiesterase can also be conferred by other means, such as the manner in which it is delivered to its target, e.g., the compound can be associated with an agent which targets it to a specific tissue or cell type having the Type IV phosphodiesterase; the manner in which it interacts with the host's metabolism and/or physiology; or synthesizing PDE inhibitor prodrugs where activation of the PDE inhibitor is accomplished by enzymes present in the desired cells or tissues but absent in others.

The specific inhibition of a Type IV phosphodiesterase can be measured conventionally, e.g., according to the methods described in Reeves et al., *Biochem. J.*, 241:535-541, 1977; by macrophage assay, as described, e.g., in Schade et al., *Europ. J. Pharmacol.*, 230:9-14, 1993; or WO 93/19068. For a review of phosphodiesterase specificity and how to determine it, see, e.g., Nicholson et al., *Trends Pharmacol. Sci.*, 12:19-27 (1991).

The activity of this invention of Type IV phosphodiesterase inhibitors such as Rolipram can be detected, for example, in animals suffering from Experimental Allergic Encephalomyelitis (EAE), an experimental T-lymphocyte initiated disease of the CNS. It can be produced, e.g., in rodents, guinea pigs, rabbits, and primates, by, e.g., immunizing animals with myelin, e.g., from a human brain, and/or corticosteroid administration over a long period of time. It can also be produced by injecting an animal with T-lymphocytes obtained from an animal suffering from EAE.

In particular, the activity can be detected in *Callithrix jacchus* (common marmoset) which has been immunized with myelin, e.g., from a human brain. The *Callithrix jacchus*

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develops EAE with essentially similar histopathology and neurological symptoms as those at certain stages of the human disease, MS.

The present invention generally relates to the treatment of MS with a combination of a PDE IV inhibitor with an interferon derivative, a prostane derivative, a glucocorticoid, an immunosuppressant, a lipoxygenase inhibitor, a leukotriene antagonist, an antiinflammatory substance, a peptide derivative or a calcipotriol or analog thereof.

A preferred combination consists of a PDE IV inhibitor and an interferon derivative, a prostane derivative or a leukotriene antagonist, e.g., betaserone, iloprost, cicaprost, or 5-[(E)-(2S)-2-((1E,3E)-(5S)-5-hydroxy-6,6-trimethylene-9-phenyl-1,3-nona diene-8-inyl)-cyclohexylidene]-pentanoic acid or esters thereof.

The pharmaceutical compositions according to the present invention are prepared conventionally, comprising substances which are customarily used in pharmaceutical, e.g., see Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing Company (1990), including excipients, carriers, adjuvants and buffers. The compositions can be administered, e.g., parenterally, enterally, orally, intramuscularly, topically, subcutaneously, intravenously, by aerosol, intrathecally directly into the cerebral spinal fluid of the CNS, or preferably by sustained release using, e.g., an implanted mini-osmotic pump (e.g., the ALZET pump manufactured by ALZA Corporation, P. O. Box 10950, Palo Alto, CA 94303), or other routes useful to achieve an effect.

Conventional excipients include pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral, enteral or topical application which do not deleteriously react with the agents. Suitable pharmaceutically acceptable adjuvants include, but are not limited to, water, salt solutions, alcohols, gum arabic, vegetable oils, polyethylene glycols, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil,

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fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxy-methylcellulose, polyvinyl pyrrolidone, cyclodextrins, etc. The pharmaceutical preparations can be sterilized and, if desired, mixed with stabilizers, 5 wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, flavoring and/or aromatic substances, etc., which do not react deleteriously with the active compounds.

For parenteral application, particularly suitable are 10 injectable sterile solutions, preferably oil or aqueous solutions, as well as suspensions, emulsions or implants, including suppositories. Ampoules are convenient unit dosages.

For enteral application, particularly suitable are 15 tablets, dragees, suppositories or capsules having talc and/or a carbohydrate carrier or binder. The carrier may be lactose, corn starch, potato starch or a combination thereof. A syrup or elixir may be used when a sweetened vehicle is employed.

The compositions can also be formulated in an aqueous 20 solution, optionally with the addition of additives customary in galenicals, for example, buffers; electrolytes such as sodium chloride; antioxidants such as ascorbic acid; adjuvants, e.g., methyl cellulose, lactose and mannitol and/or surfactants, e.g., lecithins and Tweens and/or aromatic 25 substances for flavoring, e.g., ethereal oils.

Amounts of Type IV phosphodiesterase inhibitors and drug combinations can be determined routinely based on the information given herein, e.g., using the EAE model. However, any amount which is effective in treating MS can be 30 administered to ameliorate or treat the disease. Dosages are determined conventionally, see, e.g., Remington's *Pharmaceutical Sciences*, 18th ed., Mack Publishing Company (1990). The composition may be administered in a single dose 35 unit or in multiple dosages administered, e.g., twice, three, or four times a day, or by an osmotic pump, which delivers the drug(s) continuously. A Type IV phosphodiesterase inhibitor can be administered at the same time as the anti-inflammatory,

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immunomodulatory, etc., drug in a single or separate dosage unit, or the drugs can be administered at a different time or, e.g., sequentially.

5 The exact dose of any component or combination to be administered is determined by the attending clinician and is dependent, e.g., on the potency of the compound administered, the age, weight, condition, and response of the patient.

10 Generally, PDE IV inhibitors are administered alone in amounts of about 0.005 - 2 mg/kg/day, preferably 0.1 -.7 mg/kg/day or 0.5 mg/kg/day, more preferably 0.005 - 0.1 mg/kg/day and the immuno-modulatory or anti-inflammatory, etc., is administered alone in amounts of, e.g., about 0.01 µg/kg/day for a prostacyclin or to about 10 mg/kg/day for a steroid. According to the present invention, the latter can  
15 be administered in lower doses than would be expected for purely additive effects, e.g., about 0.0005 to about 0.01 mg/kg/day for a PDE IV inhibitor and about 0.001 µg/kg/day to about 1 mg/kg/day for an immunomodulatory or anti-inflammatory drug.

20 Since the present invention relates to treatment of MS with a combination of active ingredients wherein said ingredients can be administered separately, the invention also relates to combining separate pharmaceutical composition in kit form. The kit form is particularly advantageous when the separate components are administered in different dosage forms (i.e., oral and parenteral) or are administered at different dosage intervals.

25 Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative and not limitative of the remainder of the disclosure in any way whatsoever.

30 In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius; and, unless otherwise indicated, all parts and percentages are by weight.

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Brief Description of the Drawings

Various other objects, features, and attendant advantages of the present invention will be more fully appreciated as the same becomes better understood when considered in conjunction with the accompanying drawings, in which like reference characters designate the same or similar parts throughout the several views and wherein:

Figure 1 shows the prevention of Experimental Allergic Encephalomyelitis (EAE) by Rolipram in a marmoset. A, B, and C received Rolipram (10 mg/kg) in DMSO; D and E received an equivalent volume of DMSO. Marmosets immunized with human spinal cord homogenate received either Rolipram or placebo five days after immunization.

Figure 2 shows the treatment with Rolipram of marmoset having EAE.

Examples

EXAMPLE 1

Rolipram was produced by Schering AG (Berlin) and is comprised of (+) and (-) racemates of 4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidinone. It was dissolved in dimethylsulfoxide (DMSO) at 20 mg/ml.

Human brain white matter homogenate was prepared from autopsy material in complete Freund's adjuvant (CFA) containing *M. tuberculosis* (strain H37 Ra).

Bordetella pertussis vaccine was obtained from the Massachusetts Public Health Department, Biological Laboratories, Boston, Massachusetts.

Zofran was obtained from the University of California Medical Center Pharmacy.

The marmosets were purchased from the New England Regional Primate Research Center and were maintained and cared for in accordance with the guidelines of the Internal Animal Care and Use Committee of the University of California, San Francisco.

Animals were immunized with human brain white matter homogenate (200 mg) in CFA containing 3 mg/ml killed *M.*

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tuberculosis (H37 Ra strain) by intradermal injection (0.6 ml) over four sites on the doral axilla and inguinal region. On the day of immunization and again 2 days later  $10 \times 10^{10}$  inactivated *Bordetella pertussis* (*Bordetella pertussis* vaccine) were infused intravenously in 10 ml saline.

On day 5, following immunization, animals were injected subcutaneously in the back of the neck with DMSO (placebo) or with DMSO containing Rolipram to give a dose of 10 mg/kg. Treatment with DMSO or DMSO with Rolipram was preceded 20 min. by an injection of 0.3-0.6 mg/kg Zofran intramuscularly (Ondansetron Hydrochloride, Glaxo) to prevent salivation, vomiting, excessive grooming, and head twists. Such treatments were repeated every 48 hours throughout the study.

Animals were observed daily and subjected to a standardized scoring system to record the severity of clinical symptoms:

0. Normal
1. Lethargy, anorexia, weight loss
2. Ataxia, tremor
3. Blindness, paraplegia or hemiplegia
4. Quadraparesis or quadriplegia
5. Moribund

At various times, animals were anesthetized and subjected to MRI.

**25      Experiment 1: Prevention of EAE by Rolipram Treatment**

Marmosets were immunized with spinal cord homogenate as described. On day 5, following immunization, three marmosets received Rolipram (10 mg/kg) in DMSO. See Figure 1, A, B, and C. Two marmosets received an equivalent volume of DMSO after the same interval. See Figure 1, D and E. The treatment was repeated every 48 hours.

The animals treated with DMSO (placebo) developed clinical symptoms consistent with EAE 15 days following immunization; see Figure 1, D and E. None of the Rolipram treated animals developed symptoms during the 8 week interval of observation; see Figure 1, A, B, and C.

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Magnetic Resonance Imaging (MRI) analysis showed that the two animals with EAE symptoms developed one or more lesions in the brain which "enhanced" with Magnevist (gadolinium, DTPA), indicating an active edematous response consistent with the 5 vascular inflammatory lesions seen in EAE or MS (Alvord, etc.). None of the Rolipram treated animals developed detectable lesions during the 8 week interval of observation.

**Development of EAE After Withdrawal of Rolipram**

On day 60, following immunization, the treated animals 10 were removed from treatment and observed for signs of EAE. Two marmosets began to show clinical signs of EAE on day 17, following withdrawal of Rolipram.

**Experiment 2: Treatment of Active EAE with Rolipram**

In the previous experiment, it was clearly demonstrated 15 that Rolipram could prevent EAE. It is of interest to determine if Rolipram can also affect active EAE. In this experiment, a marmoset was immunized as previously described, allowed to develop symptoms of chronic EAE and subsequently treated with Rolipram. The animal was treated with escalating 20 doses of Rolipram in DMSO administered as described in the previous experiment. The physical symptoms were monitored as described and MRI analysis was done at times before and after treating (Figure 2).

The animal showed marked improvement on day 10 after 25 initiating treatment. The animal showed MRI improvement on day 14 following initiating Rolipram treatment and, from that time, the condition stabilized with slower improvements.

The results of Experiment 1 indicate that Rolipram treatment blocked the neurological signs of EAE. The MRI 30 results indicate that the inflammatory response was blocked and demyelination did not occur. The untreated control animals developed clear signs of EAE and inflammatory lesions as indicated by MRI analysis. The fact that treated animals developed EAE when removed from treatment showed that the 35 immune response to brain homogenate had occurred sufficiently

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to initiate the disease; however, some subsequent step in pathogenesis was blocked.

The results of Experiment 2 indicate that Rolipram treatment can inhibit active disease.

5      **EXAMPLE 2**

To assess the ability of rolipram alone or in various combinations as described to modify autoimmune processes, we investigated its influence on TNF production *in vitro* by MBP-specific T-cell lines from MS patients and Lewis rats. MBP is 10 a major candidate antigen in MS, and T-cell-mediated immunity is of crucial importance in its pathogenesis. Similar to EAE, MBP-specific T-cells in humans are often cytotoxic, of Th1 type secreting interferon (IFN)-gamma and TNF/LT, and recognize epitopes that are also encephalitogenic in EAE.

15      Rolipram selectively inhibited TNF production by human MBP-specific T-cell lines (TCL) in a dose-dependent manner alone and in combination.

Similar results were found using an encephalitogenic CD4+ MBP-specific rat TCL (L1402). TNF/LT (lymphotoxin) production 20 measured in a cytotoxicity bioassay was inhibited in a dose range comparable to the human lines. Moreover, inhibition was stereospecific, with the (-)-enantiomer being 55 times more effective than the (+)- enantiomer. The EC<sub>50</sub> of (-)-rolipram, (+)-rolipram, and (-)-rolipram given alone were 20 nM, 280 nM, 25 and 1100 nM, respectively. Previous investigations had shown that inhibition of cAMP PDE by rolipram is stereospecific. *In vitro* and *in vivo* binding data in mouse and rat forebrain tissue with <sup>3</sup>H-rolipram proved for the (-)-enantiomers a 15-30 times higher affinity than the (+)-enantiomers. In line with 30 these findings, our data strongly suggest that rolipram inhibits TNF/LT production in human and rat autoreactive T-cells by an intracellular cAMP PDE dependent mechanism.

TNF and LT may both be produced by autoactive T-cells. CD4+ cells have been reported to be the major source of TNF in 35 autoimmune insulitis of NOD mice. The cytokine bioassay for

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TNF/LT detection employed here is sensitive to TNF and LT, but is 200 times more sensitive to the former.

The results of our *in vivo* findings prompted us to perform treatment experiments in EAE after active immunization 5 (aEAE) and adoptive cell transfer (tEAE) in Lewis rats. When rolipram was administered from day 7 through day 23 in aEAE as monotherapy or in various combinations, the appearance of neurological symptoms was completely prevented. In clinically manifest EAE, treatment was started within 6 hours of the 10 onset of symptoms. In the treated group, disease did only progress moderately, whereas the controls developed severe EAE. None of the rolipram-treated animals developed grade 4 (paraplegia), whereas 4 to 7 animals in the vehicle-treated control group reached this level of impairment in one typical 15 experiment. In tEAE similar effects were observed.

Prophylactic treatment resulted in only minor symptoms with a mean maximum score (MMN) of  $0.3 \pm 0.11$  ( $n = 5$ ) in the treated group, as compared to  $2.5 \pm 0.25$  ( $n = 5$ ) in the controls ( $p < 0.01$ ). Treatment after onset of symptoms also lead to a 20 marked reduction in maximum severity (treated group: MMS  $0.7 \pm 0.10$ ,  $n = 5$ ; vehicle treated matched controls  $2.45 \pm 0.56$ ,  $n = 5$ ,  $p < 0.01$ ).

In order to distinguish further between a long-term prophylactic or a temporary suppressive effect, animals 25 received the drug from the day of active immunization until day 11. With this regimen aEAE in treated animals was delayed by 3.5 days, but disease severity and duration was otherwise similar compared to the controls. This indicates that suppression of EAE and presumably TNF/LT production is 30 temporary, and deletion of autoreactive T-cells by rolipram, as, e.g., in the case of cyclophosphamide, is therefore unlikely.

Histological analysis was performed on selected animals with aEAE. There were only few and mild cellular lesions in 35 the prophylactically treated animals. By contrast, two or three animals that were treated after onset of clinical signs showed cellular infiltrates similar to those in the controls.

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Previous investigations have shown that inflammatory infiltrates in the central nervous system do not necessarily correlate with the degree of neurological deficit. In a study on EAE, induced by myelin oligodendrocyte glycoprotein (MOG)-specific T-cells, the lack of neurological signs was ascribed to a decrease of macrophages and parenchymal inflammation, whereas perivascular inflammation and the synthesis of TNF, IFN-gamma, and interleukin-6 was clearly present. In our system, however, the timely onset of paralysis and the morphologically similar appearance of infiltrates in some of the treated animals argues against such a phenomenon. We propose that during rolipram treatment of clinically manifest EAE, suppression of local TNF production in addition to its other effects is crucial regardless of the discrepancy between the histological and clinical scores. Using in-situ hybridization, it was shown recently that the present of TNF expressing cells in the CNS correlates well with the clinical signs in EAE. Using this approach it should be possible to identify the rolipram-sensitive cell types in EAE and MS lesions - inflammatory cells, glial cells, or both.

In contrast, rolipram by its many effects is expected to be of great therapeutic use in MS and other patients, especially in appropriate combinations, as shown by these and other experiments and as indicated by the considerations already discussed.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

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From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the  
5 invention to adapt it to various usages and conditions.

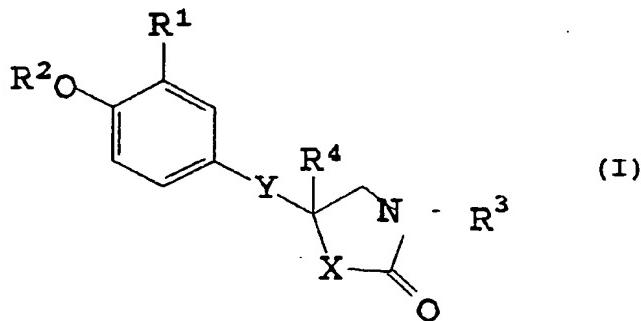
CLAIMS

We claim:

1. A pharmaceutical composition for treating MS, Guillan-Barre's Syndrome, virus-, bacteria-, or parasite-related demyelinating diseases, encephalopathies related to HIV, meningococcal or toxoplasma infections, central malaria, or Lyme's Disease, comprising an effective amount of a combination of a PDE IV inhibitor and an anti-inflammatory or immunomodulatory drug and a pharmaceutically acceptable carrier.

2. A pharmaceutical composition according to claim 1 for treating MS.

3. A composition of claim 1, wherein the PDE IV inhibitor is a compound according to formula I



wherein

R<sup>1</sup> is C<sub>1-6</sub>-alkyl, a heterocyclic ring, or OR<sup>5</sup>; and

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- R<sup>5</sup> is C<sub>1-6</sub>-alkyl, C<sub>3-7</sub>-cycloalkyl, C<sub>2-6</sub>-alkenyl, C<sub>3-7</sub>-alkinyl, C<sub>3-7</sub>-cycloalkyl-C<sub>1-2</sub>-alkyl, aryl, aralkyl, a heterocyclic ring or C<sub>1-6</sub>-alkyl substituted by one or more halogen atoms, hydroxy, carboxy, C<sub>1-4</sub>-alkoxy, C<sub>1-4</sub>-alkoxycarbonyl, or an optionally alkyl substituted amino group;
- R<sup>2</sup> is C<sub>1-4</sub>-alkyl, C<sub>2-4</sub>-alkenyl, or C<sub>2-4</sub>-alkinyl;
- R<sup>3</sup> is a hydrogen atom, C<sub>1-6</sub>-alkyl, aryl, aralkyl, or aryl optionally substituted by one or two methyl groups or C<sub>1-6</sub>-alkanoyl;
- R<sup>4</sup> is a hydrogen atom or C<sub>1-6</sub>-alkyl;
- Y is a direct bond or a CH<sub>2</sub> group;
- X is CH<sub>2</sub>, CH<sub>2</sub>-CH<sub>2</sub>, NH, or an oxygen atom; and pharmaceutically acceptable salts thereof.

4. A composition of claim 1, wherein the PDE IV inhibitor is Rolipram.

5. A composition of claim 1, wherein the anti-inflammatory or immunomodulatory drug is an interferon derivative, a prostane compound, a leukotriene antagonist, a peptide compound, or a calcipotriol or analog thereof.

6. A composition of claim 1, wherein the anti-inflammatory or immunomodulatory drug is Iloprost.

7. The use of a PDE IV inhibitor in combination with a anti-inflammatory or immunomodulatory drug for the preparation of a pharmaceutical composition useful in the treatment of MS.

8. A method of preventing or treating multiple sclerosis comprising administering to a host in need thereof an effective amount of a composition according to claim 1.

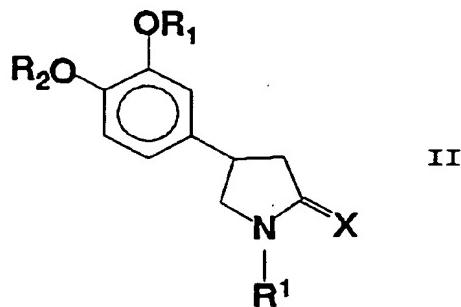
9. A method according to claim 8, wherein the time between or the severity of symptoms of the episodic recurrences of the multiple sclerosis is ameliorated.

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10. A method according to claim 8, wherein an inflammatory lesion associated with said multiple sclerosis is prevented or treated.

11. A method according to claim 8, wherein the appearance of an inflammatory lesion associated with said multiple sclerosis is slowed.

12. A method of preventing or treating multiple sclerosis, comprising administering to a host in need thereof an effective amount of a compound according to formula II



wherein:

R<sub>1</sub> and R<sub>2</sub> each are alike or different and are C<sub>1-18</sub>-alkyl with at least one being other than methyl, a heterocyclic ring, or C<sub>1,5</sub>-alkyl substituted by one or more of halogen atoms, hydroxy, carboxy, alkoxy, alkoxycarbonyl or an amino group;

R' is a hydrogen atom, alkyl, aryl or acyl; and X is an oxygen atom or a sulfur atom.

13. A method of claim 12, wherein said compound is 4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidinone.

14. A method according to claim 12, wherein one of R<sub>1</sub> and R<sub>2</sub> is methyl, and the other is C<sub>3,7</sub>-cycloalkyl.

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15. A method of claim 12, wherein the time between or the severity of symptoms of episodic recurrences of multiple sclerosis is ameliorated.

16. A method according to claim 12, wherein an inflammatory lesion associated with said multiple sclerosis is prevented or treated.

17. A method according to claim 12, wherein the appearance of an inflammatory lesion associated with said multiple sclerosis is slowed.

18. A method according to claim 12, wherein said compound is a Type IV phosphodiesterase.

19. A method of preventing or treating multiple sclerosis comprising administering to a host in need thereof an effective amount of a Type IV phosphodiesterase inhibitor.

20. A method according to claim 19, wherein the time between or the severity of symptoms of the episodic recurrences of the multiple sclerosis is ameliorated.

21. A method according to claim 19, wherein an inflammatory lesion associated with said multiple sclerosis is prevented or treated.

22. A method according to claim 19, wherein the appearance of an inflammatory lesion associated with said multiple sclerosis is slowed.

23. A method of preventing or treating multiple sclerosis comprising administering to a host in need thereof an effective amount of 4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidinone.

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24. A kit comprising in separate containers in a single package pharmaceutical compositions for use in combination to treat MS which comprises a PDE IV inhibitor and, in a second container, a pharmaceutical composition comprising an anti-inflammatory and immunomodulatory drug.

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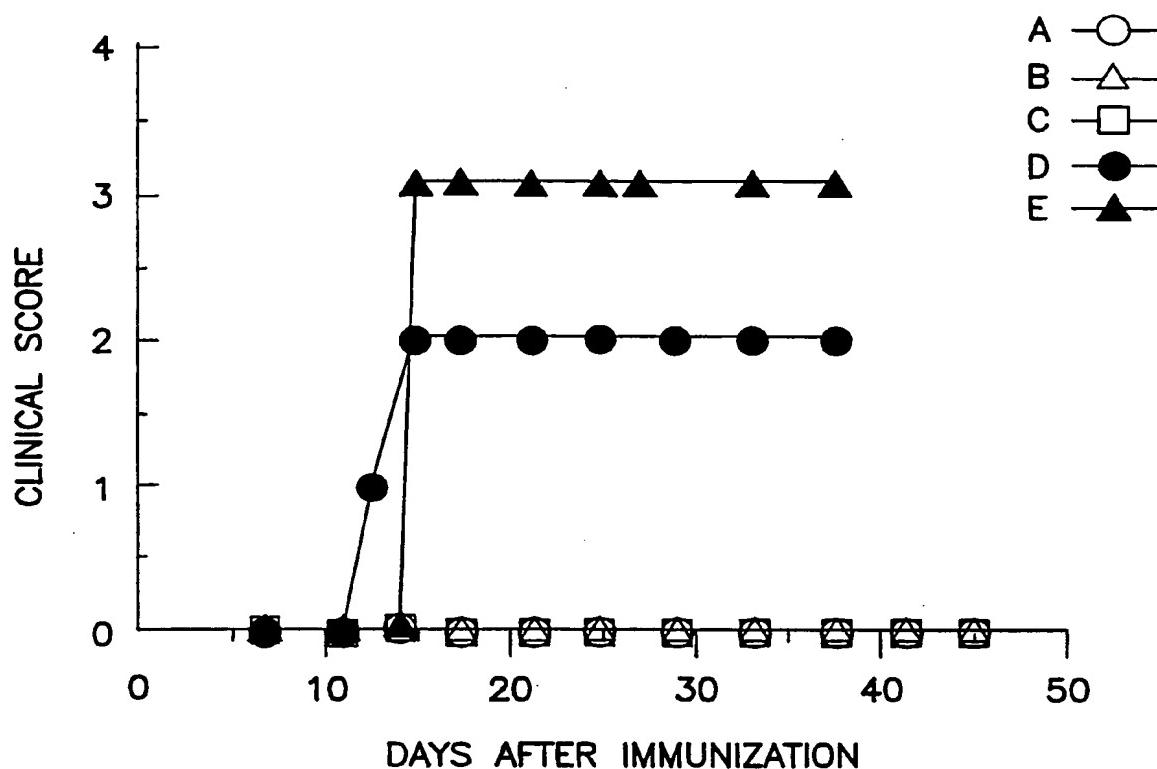


FIG. I

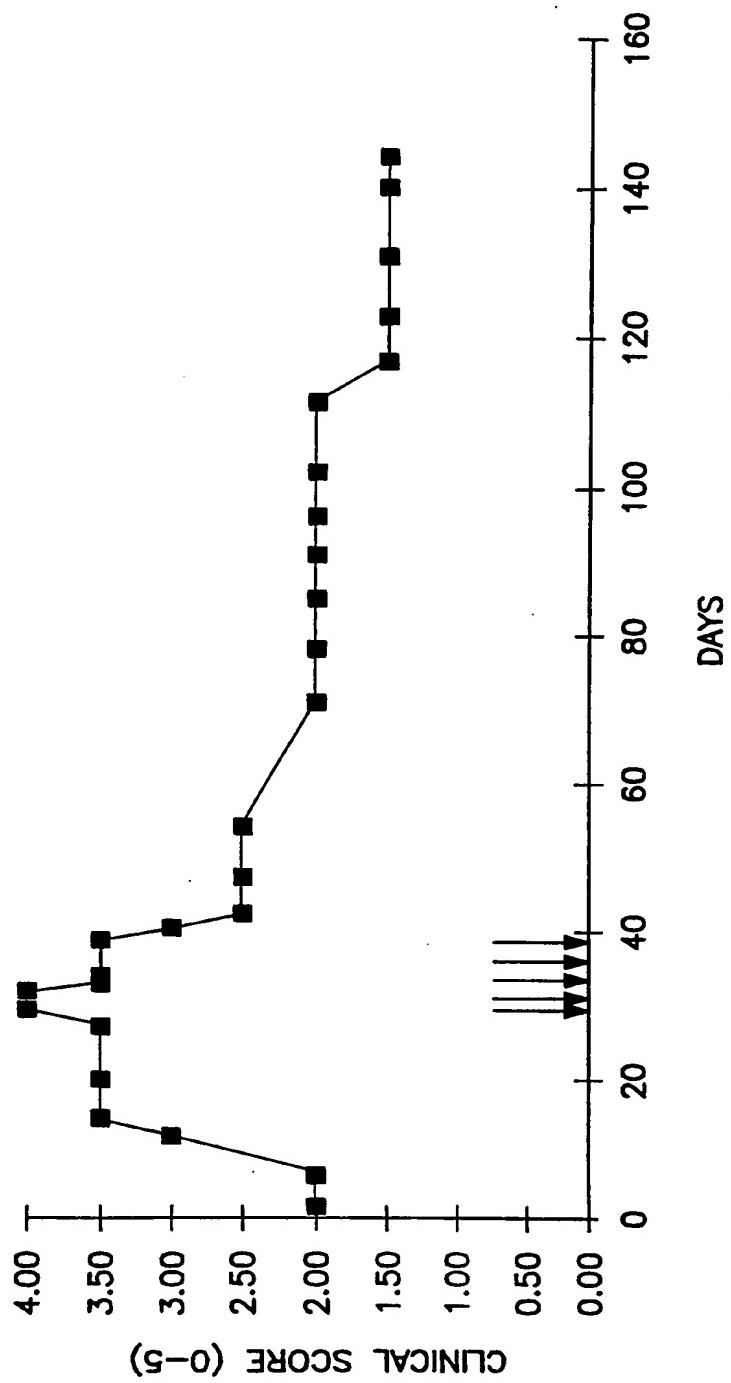


FIG. 2

SUBSTITUTE SHEET (RULE 26)

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IB 95/00332

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K31/40 // (A61K31/40, 31:00, 38:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	J. NEUROBIOLOGY, vol. 54, no. 1-2, 1994 page 198 SOMMER ET AL. 'Tumor-necrosis factor-directed therapy of autoimmune encephalomyelitis by the phosphodiesterase IV inhibitor rolipram' * see abstract no. P15.08 ---	12-23
X	ACTA NEUROLOGICA SCANDINAVICA, vol. 88, no. 2, 1993 pages 97-99, NATAF ET AL. 'Pentoxifylline inhibits experimental allergic encephalomyelitis' * see whole document * * " *	19-22
Y	---	7-23
	-/-	

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
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- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search  21 July 1995	Date of mailing of the international search report  21.08.95.
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 cpo nl, Fax (+31-70) 340-3016	Authorized officer  Iseret, B

## INTERNATIONAL SEARCH REPORT

Interr.	ai Application No
PCT/IB 95/00332	

## C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EUR. J. PHARMACOL., vol. 230, no. 1, 5 January 1993 pages 9-14, SCHADE ET AL. 'The specific Type III and IV Phosphodiesterase inhibitor zardaverine suppresses formation of tumor necrosis factor by macrophages' * see whole document, in particular Fig. 2 and Table 2* * " *	1-6,24
Y	----- WO,A,92 19594 (SMITH-KLINE BEECHAM ) 12 November 1992 * see claims 1-12 * -----	7-23
Y	-----	12-23

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 95/00332

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9219594	12-11-92	AU-A-	1917092	21-12-92
		CN-A-	1067244	23-12-92
		EP-A-	0584208	02-03-94
		JP-T-	6507405	25-08-94